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Moderate Renal Function Impairment Does Not Affect Outcomes of Reduced-Intensity Conditioning with Fludarabine and Melphalan for Allogeneic Hematopoietic Stem Cell Transplantation

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Nonrelapse mortality (NRM) after reduced-intensity allogeneic transplants is likely to be influenced by abnormalities in renal function. We studied 141 patients diagnosed with acute myelogenous leukemia (AML) (n = 131) or high-risk myelodysplastic syndrome (MDS) (n = 10) who underwent allogeneic transplantation with fludarabine (Flu)/melphalan (Mel)-based regimens and hypothesized that moderate to mild renal function impairment increases NRM in this setting. Flu dose consisted of 25-30 mg/m^2 for 4 days and Mel dose was 100-180 mg/m^2. Donors were HLA-compatible siblings (n = 69) and matched unrelated donors (n = 72). Disease status at transplantation was complete remission (n = 56, 40%) or active disease (n = 85, 60%). The influence of the estimated glomerular filtration rate (GFR) measured before transplantation on outcomes was analyzed. GFR was estimated by both the Cockcroft-Gault (CG) and the modified diet in renal disease (MDRD) equations, using the creatinine value obtained prior to starting chemotherapy. Evaluated outcomes were overall survival (OS), NRM, and treatment-related mortality (TRM) at day 100 and 1-year posttransplantation. Median age was 55 years (range: 21-74 years); 59% of the patients were male. Estimated GFR by CG was ≥90 for 45 (32%), 60-89 for 78 (55%), and <60 for 18 (13%) patients. When estimated by MDRD, GFR was ≥90 for 65 (46%), 60-89 from 66 (47%), and <60 for 10 (7%) patients. The majority of patients by both estimations had a GFR between 60 and 89 (n = 78 by CG and n = 66 by MDRD) with no difference in the evaluated outcomes between this group and the subgroup of patients with a GFR <60 ($P > .05$). There were no differences in OS and NRM at day 100 and 1-year posttransplantation in the 3 groups by any GFR estimation method. In conclusion, a mild to moderate decrease in GFR was not associated with an increase in NRM.

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INTRODUCTION

Renal injury is a common complication of hematopoietic cell transplantation (HCT), and is associated with increased morbidity and mortality [1,2]. Consequently, impairment of renal function is often used as an exclusion criterion when selecting patients who undergo HCT. Acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) are diseases of the elderly, a population usually with some degree of renal impairment, frequently worsened by previous chemotherapy and exposure to a variety of nephrotoxic drugs.

Nonmyeloablative (NMA) conditioning regimens were developed as less toxic modalities of treatment for the elderly population and those with serious comorbidities who are not eligible for standard myeloablative (MA) HCT [3]. As proposed by Champlin et al. [4,5], the definition of a truly nonablative regimen is one that can be given routinely without stem cell support, with neutrophil recovery within 28 days, and one in which mixed chimerism can be routinely detected early after transplantation. Regimens that cannot be

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safely administered without stem cell support have been termed reduced-intensity conditioning (RIC) [6]. At M.D. Anderson Cancer Center, we use the combination of a purine analog (fludarabine [Flu]) with an alkylating agent (melphalan [Mel]) [3,6-11].

We hypothesized that patients with AML/MDS and renal impairment before the administration of the Flu/Mel regimen would have worse outcomes, including higher nonrelapse mortality (NRM), than those with a normal renal function. The hypothesis was investigated in a homogeneous patient population including only AML/MDS patients that received RIC and allogeneic HCT.

METHODS

Eligibility

Patients were included in this retrospective analysis if they had either AML or high-risk MDS and had undergone an allogeneic HCT from an HLA-compatible donor with an RIC regimen with Flu/Mel. Patients were treated under consecutive protocols, and were eligible to receive Flu/Mel if older than 50 years, or in the presence of clinical comorbidities that precluded the use of myeloablative conditioning. Patients were also selected on the basis of having a creatinine level <1.6 mg/dL. Patients that received a previous allogeneic transplant were excluded. From August 1996 until May 2006, a total of 141 patients met these eligibility criteria and were included in the present analysis.

Reduced-Intensity regimen

All subjects signed written informed consents, and their treatment protocols and this study were approved by our institutional review board (IRB). Patients received Flu 25 to 30 mg/m^2 for 4 to 5 days in combination with melphalan Mel 100, 140, or 180 mg/m^2 total dose. Antithymocyte globulin (ATG) was added for recipients of unrelated (UD) or mismatched related donor HCT. Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus (FK506, Prograf, Fujisawa, Deerfield, IL) and methotrexate (MTX) 5 mg/m^2 i.v. on days 1, 3, 6, and 11 after transplantation for all but 2 patients. Tacrolimus levels were monitored 3 times a week and kept at therapeutic ranges of 5 to 10 ng/dL during the first 100 days and then tapered at the discretion of the primary physician depending on donor type, disease status at time of transplantation, presence or absence of GVHD, and presence of residual donor cells as documented by chimerism or cytogenetic analysis. Tacrolimus target levels and MTX doses were similar regardless of baseline renal function.

Antibacterial, antifungal, and antiviral prophylaxis consisted of trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* prophylaxis, acyclovir or valacyclovir for herpes simplex virus (HSV) prophylaxis, and surveillance cytomegalorivus (CMV) antigenemia testing for all patients with preemptive use of ganciclovir in the event of a positive antigenemia test. All patients received filgrastim (granulocyte colony-stimulating factor [G-CSF]) (Neupogen, Amgen, Thousand Oaks, CA) 5 mg/kg s.c. daily from day +7 until achievement of an absolute neutrophil count (ANC) above 1.5×10^9/L for 3 days. Packed red blood cells were administered to maintain hemoglobin levels greater or equal to 8 g/dL. Platelet transfusions were administered to keep the platelet count at a level of $\geq 10 \times 10^9$/L. All blood products were filtered and irradiated. Donor stem cells or bone marrow (BM) were procured using standard mobilization protocols and pheresis techniques. The stem cells or BM from all related donors were collected at the M.D. Anderson Cancer Center, and they were processed according to current institutional guidelines and protocols. All healthy donors signed written informed consent for the procedure. BM procured from UD was obtained through the National Marrow Donor Program (NMDP) according to applicable guidelines at the time of procurement. As required by the NMDP, donors gave consent at the donor center after an extensive screening and information process.

Renal Function Assessment

Baseline glomerular filtration rate (GFR) was estimated the day prior to the conditioning regimen and in other time points before and after HCT using both the abbreviated modified diet in renal disease (MDRD) equation: GFR (mL/min/1.73 m^2) = $186 \times P_{cr}^{-1.154} \times age^{-0.203} \times (1.212 \text{ if black}) \times (0.742 \text{ if female})$ and the Cockcroft-Gault (CG) equation, GFR (mL/min/1.73 m^2) = $(140 - age) \times (weight)/(P_{Cr} \times 72) \times (0.85 \text{ if female})$, where P_{cr} is the plasma creatinine level [12,13]. Pretransplantation baseline renal function was classified into 5 stages, as suggested by the National Kidney Foundation (NKF) [12], and patients were divided into 3 risk groups according to their GFR: <60 (NKF 3, 4, and 5), 60-89 (NKF 2), ≥90 (NKF 1) mL/min/1.73 m^2.

Statistical Considerations

The primary endpoints were overall survival (OS), NRM, and treatment-related mortality (TRM) on day +100 and 1 year after transplantation. Outcomes were estimated starting on the day of HCT. NRM was defined as death occurring in the absence of progression or relapse of malignancy. TRM was defined as NRM excluding deaths attributed to GVHD [14]. Actuarial OS was estimated by the method of Kaplan-Meier. The cumulative incidence method accounting for competing risks was used to estimate the rates of TRM, NRM, absolute creatinine level above 1.5 mg/dL, and requirement

Table 1. Patient Characteristics

Age (median)	55 years (21-75)	
Sex	Male	83 (59%)
	Female	58 (41%)
Diagnosis	AML	131 (93%)
	High-risk MDS	10 (7%)
Disease status	Active disease	85 (60%)
at HCT	Remission	56 (40%)
Donor	Related	69 (49%)
	Matched unrelated	72 (51%)
Stem cell source	Bone marrow	74 (52%)
	Peripheral blood	67 (48%)
Baseline GFR (mL/min/1.73 m^2)	< 60	10 (7%)
MDRD	60-89	66 (47%)
	≥90	65 (46%)
Cockroft-Gault	<60	18 (13%)
	60-89	78 (55%)
	≥ 90	45 (32%)

AML indicates acute myelogenous leukemia; MDS, myelodysplastic syndrome; GFR, glomerular filtration rate; MDRD, Modified Diet in Renal Disease.

of dialysis. Outcomes according to pretransplantation renal function were compared on univariate analysis using the Cox's proportional hazards model. Multivariate analysis was not possible because of sample size considerations. All *P*-values presented are 2-sided. Statistical analyses were carried out using Stata 8.0.

RESULTS

The demographic and transplant characteristics of the study cohort (N = 141) are described in Table 1. All patients received allografts for AML/MDS after an RIC regimen with Flu/Mel. The median age at transplantation was 55 years (range: 21-75 years) and 69 patients (49%) received hematopoietic cells from HLA-matched related donors. GFR (as measured by the MDRD equation) was <60 in 10 patients (7%), between 60 and 89 in 66 patients (47%), and ≥90 in 65 patients (46%). The corresponding proportions per the CG equation were 13%, 55%, and 32%. Demographic and disease-related characteristics were comparable in patients with a CG <60, 60-89 and ≥90, except for age, which was older in the group with CG <60 (median: 61 years, $P = .03$) as seen in Table 2.

Most of the patients with renal function impairment, had it for at least 1 month prior to transplantation. For the subgroup with baseline GFR <60 (calculated using the MDRD method), the median GFR was 56 (range: 39-77), and half of the patients had a GFR <60. As measured by the CG method, patients with baseline GFR <60 had a median GFR of 56 (range: 23-106); 75% of the patients in this group had a GFR <60 a month prior to transplantation. These patients had several risk factors for renal impairment. The hematopoietic stem cell transplantation-specific comorbidities index (HCT-CI) [15] score was equal to or greater than 3 in 16 cases. Coexisting comorbid conditions included cardiac disease (heart failure, n = 3; arrhythmia, n = 3; coronary artery disease, n = 5), and hypertension (n = 10). In addition, 1 patient had diabetes, and 8 patients had a history of prior treatment for a malignancy.

We investigated if the administration of commonly used nephrotoxic drugs (including amphotericin B, foscarnet, vancomycin, and gentamicin) had an impact on GFR on day 100 or day 180 after transplantation. For this purpose, we collected data for the subset of patients who had GFR ≥60 (as measured by the MDRD method) at the time of transplantation (N = 131) and who had survived up to at least 100 (n = 98/131) and 180 (n = 73/131) days. Survivors were then divided into 2 groups, according to GFR on transplant day 100 and 180 (Table 3). Chi-square comparisons showed that the proportion of patients who had received nephrotoxic drugs was similar in patients with GFR ≥60 and those with GFR <60 on both time points, although the group with worse renal function had a statistically insignificant higher proportion of patients that received foscarnet and amphotericin. The proportion of patients who received 1, 2, or 3 drugs was comparable in patients with GFR ≥60 or <60 both on 100 and 180 days after HCT.

Tables 4 and 5 show outcomes according to GFR estimated by the CG and MDRD equations, respectively. Pretransplantation GFR estimated by both the

Table 2. Patient Characteristics According to the Glomerular Filtration Rate (GFR) Estimated by the Cockroft-Gault (CG) Method

	CG <60 (n = 18)	CG 60-89 (n = 78)	CG ≥90 (n = 45)	CG <60 versus ≥60 (*P* value)
Median age (range)	61 (25-74)	57 (30-72)	47 (21-74)	.03
Age >50 years	72%	82%	33%	.3
Median prior chemotherapy regimens (range)	1 (0-6)	1 (0-8)	2 (0-5)	.7
Donor type				
Related	56%	53%	40%	
Unrelated	44%	47%	60%	.4
Disease status at HCT				
CR	33%	47%	29%	
Other	67%	53%	71%	.4
Median GFR (range)	51 (27-58)	74 (60-89)	107 (90-153)	
Median absolute creatinine value (range)	1.0 (0.8-1.9)	1.0 (0.6-1.4)	0.75(0.5-1.1)	

CR indicates complete remission; GFR, golmeruler filtration rate; HCT, hematopoietic cell transplantation.

Table 3. Use of Nephrotoxic Drugs during the First 100 Days, and Renal Function 100 and 180 Days after Transplant

	GFR <60 Day 100 (%) n = 46		GFR ≥60 Day 100 (%) n = 52		*P* value
Amphotericin B					
Yes	23	50%	23	44%	
No	23	50%	29	56%	.6
Foscarnet					
Yes	20	43%	17	33%	
No	26	56%	35	67%	.3
Vancomycin					
Yes	19	41%	21	40%	
No	27	59%	31	60%	.9
Gentamicin					
Yes	2	4%	2	4%	
No	44	96%	50	96%	.6
Number of drugs					
None	8	17%	13	25%	
1	18	39%	20	39%	
2	12	26%	14	27%	
3	8	17%	5	10%	.2
	GFR <60 Day 180 (%) n = 38		GFR ≥60 Day 180 (%) n = 35		*P* value
Amphotericin B					
Yes	18	47%	14	37%	
No	20	53%	21	55%	.6
Foscarnet					
Yes	16	42%	11	29%	
No	22	58%	24	63%	.3
Vancomycin					
Yes	14	37%	13	34%	
No	24	63%	22	58%	.9
Gentamicin					
Yes	3	8%	0	0%	
No	35	92%	35	92%	.9
Number of drugs					
None	8	21%	11	29%	
1	15	39%	14	37%	
2	8	21%	6	16%	
3	7	18%	4	11%	.4

All patients had a glomerular filtration rate (GFR) ≥60 prior to transplant (n = 131).

MDRD or CG equations had no significant impact on OS, NRM, or TRM. There was a trend for a higher day +100 all-cause mortality, NRM, and TRM in patients who had a baseline MDRD level ≥60, yet this did not reach statistical significance. Patients with a mild pre-HCT renal impairment (MDRD or CG between 60 and 89) had similar outcome to those with normal renal function (MDRD or CG ≥90).

The cumulative incidence of an absolute creatinine level above 1.5 mg/dL during the first year after the transplantation was 37%, 41%, and 41% in patients with a pre-HCT CG level <60, 60-80, or ≥90, respectively (Figure 1). These rates were not significantly different ($P = .9$). Similarly, pre-HCT CG did not have a significant impact on the incidence of dialysis ($P = .08$), with a cumulative incidence of 0% in patients with the worst baseline renal function (CG <60), 15% in patients with mild renal impairment (CG 60-89), and 4% in those with normal renal function (CG ≥90). Overall, 9% (n = 13) of patients in our cohort needed dialysis (Figure 2). Ten of the dialyzed patients had a comorbidity index score ≥3. Comorbid conditions included cardiac disease (n = 5; congestive heart failure, arrhythmia, and coronary arterial disease), previous treatment for another neoplasia (n = 3), and diabetes mellitus (n = 1). Precipitating causes included drug nephrotoxicity (n = 7), sepsis (n = 1), and thrombotic thrombocytopenic purpura (n = 3). Interestingly, median GFR for the group with the worse baseline renal function remained stable after HCT (as calculated by the MDRD method): the median was 44 (range: 31-90; n = 9) and 48 (range: 48-63; n = 4), respectively, at day + 100 and at 1 year posttransplantation.

DISCUSSION

Renal failure is a common complication of any modality of HCT despite recent improvements in patient supportive care. Patients that develop kidney disease after NMA HCT may have an increased risk of mortality even if they do not require dialysis or if renal function improves [16]. The reported incidence of acute renal failure in this setting ranges from 33% to 44% within the first 100 days [17,18], whereas that of chronic kidney disease can be as high as 60% within 1 year [19]. Parikh and collaborators [17] found that the

Table 4. Outcomes and Baseline Glomerular Filtration Rate (GFR), as Measured by the Cockroft-Gault (CG) Method*

CG	100-Day mortality n (%)	HR (95% CI)	*P* value	1-Year mortality n (%)	HR (95% CI)	*P* value
All-cause mortality						
<60	4 (22%)	ref.		9 (50%)	ref.	
60-89	20 (26%)	1.12 (0.4-3.3)	.8	35 (45%)	0.8 (0.4-1.7)	.7
≥90	11 (24%)	1.04 (0.3-3.3)	.9	24 (53%)	1.0 (0.7-1.97)	.96
Non-relapse mortality						
<60	3 (17%)	ref.		5 (28%)	ref.	
60-89	16 (21%)	1.15 (0.3-3.9)	.8	26 (33%)	1.0 (0.4-2.7)	.9
≥90	9 (20%)	1.1 (0.3-4.0)	.9	14 (31%)	1.0 (0.4-2.8)	.9
Treatment-related mortality						
<60	2 (11%)	ref.		2 (11%)	ref.	
60-89	10 (13%)	1.1 (0.2-5.1)	.9	12 (15%)	1.2 (0.3-5.5)	.8
≥90	3 (7%)	0.6 (0.1-3.4)	.5	6 (13%)	1.1 (0.2-5.4)	.9

HR indicates hazard ratio; CI, confidence interval.
*Cockroft-Gault method (mL/min/1.73 m^2).

Table 5. Outcomes and Baseline Glomerular Filtration Rate (GFR), as Measured by the Modified Diet in Renal Disease (MDRD) Formula*

MDRD	100-Day Mortality n (%)	HR (95% CI)	*P*-value	1-Year mortality n (%)	HR (95% CI)	*P*-value
All-cause mortality						
<60	1 (10%)	ref.		5 (50%)	ref.	
60-89	16 (24%)	2.6 (0.3-19.4)	.4	29 (44%)	0.9 (0.3-2.2)	.7
≥90	18 (28%)	2.9 (0.4-22.2)	.3	34 (52%)	1.0 (0.4-2.6)	.96
Nonrelapse mortality						
<60	1 (10%)	ref.		3 (30%)	ref.	
60-89	13 (20%)	2.15 (0.3-16.4)	.5	21 (32%)	1.1 (0.3-3.7)	.9
≥90	14 (22%)	2.3 (0.3-17.8)	.4	21 (32%)	1.1 (0.3-3.7)	.9
Treatment-related mortality						
<60	0	ref.		1 (10%)	ref.	
60-89	9 (14%)	cannot estimate		10 (15%)	1.5 (0.2-11.8)	.7
≥90	6 (9%)	cannot estimate		9 (14%)	1.0 (0.2-11.1)	.7

HR indicated hazard ratio; CI, confidence inteval.
HR could not be estimated for some categories because of lack of events.
*Glomerular filtration rate estimated by the Modified Diet in Renal Disease method (mL/min/1.73 m^2).

mortality of patients after NMA HCT at 6 months and 1 year was associated with the severity of kidney injury. In another recent publication including 13 patients (6 of which had AML/MDS) with mildly reduced renal function before NMA allogeneic HCT, more than half of the patients had improvement of renal function after transplantation [20]. Nevertheless, renal impairment is frequently used as an exclusion criterion when selecting patients for HCT, especially when GVHD prophylaxis with a calcineurin inhibitor is contemplated. It is unclear if there is a threshold below which patients with renal failure should not receive allogeneic HCT. Furthermore, with the increasing use of calcineurin inhibitor-free GVHD prophylaxis, it is likely that renal function-based limitations established in the past will be systematically challenged in the near future.

We hypothesized that patients with a decreased baseline GFR would have worse outcomes after allogeneic transplant, but were unable to confirm this hypothesis. A mild to moderate decrease in renal function was not associated with an increase in NRM.

OS, NRM, and TRM at day +100 and at 1 year were not influenced by baseline renal function, as measured here. Our cohort had a median age of 55 years, but did not include a significant proportion of patients with severe renal failure, a reflection of the selection process that preceded transplantation. We, however, studied a homogenous population with AML/MDS treated with Flu/Mel, a chemotherapy regimen that is not markedly nephrotoxic. Our cohort was heavily pretreated and the majority of the patients were not in remission, having failed salvage chemotherapy. Previous studies analyzing renal function in the context of NMA conditioning investigated patients with a broad range of hematologic malignancies and most of them included regimens with total body irradiation (TBI) [21]. Therefore, our conclusions may not apply to other conditioning regimens.

We found a higher rate of patients requiring dialysis after transplantation than previously reported [16-18]. Nine percent of patients in our cohort needed dialysis at some point after HCT, but it is interesting to note that they did not belong to the group with the worst baseline renal function. In addition, the median GFR remained stable in the survivors belonging to the subgroup of patients with a baseline GFR <60, at 100 days and 1 year after transplantation.

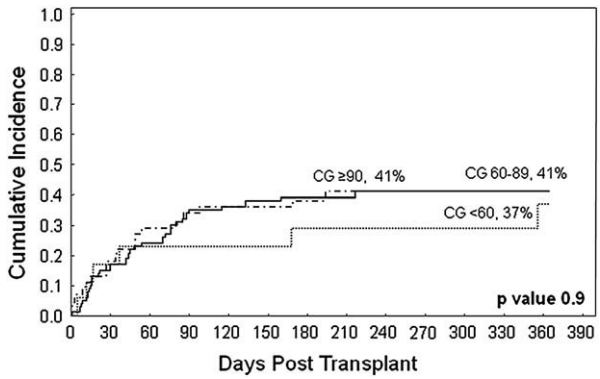

Figure 1. Cumulative incidence of a creatinine level above 1.5 mg/dL in the first year after transplantation. The GFR estimated by the CG method did not have an impact on the incidence of renal failure after transplant.

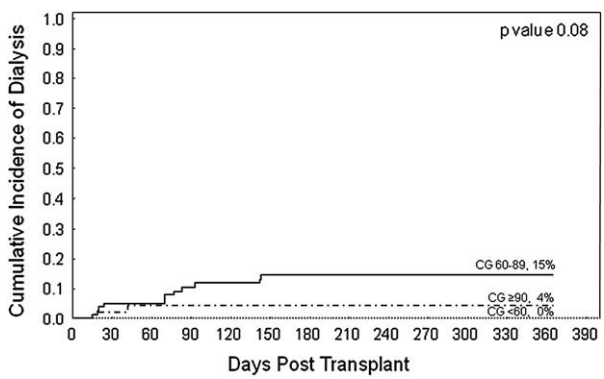

Figure 2. Cumulative incidence of renal failure requiring dialysis in the first year after transplantation. The GFR as estimated by the CG equation did not have an impact on the incidence of renal failure requiring dialysis.

There are some limitations when interpreting the results of our study. Although the population was homogeneous in terms of diagnosis and conditioning regimen, the sample size is relatively small, decreasing our ability to control for other variables known to influence renal function, such as blood pressure and medication use. However, the proportion of patients that used amphotericin, gentamicin, foscarnet, and/or vancomycin during the first 100 days after transplantation was similar among patients with GFR below and above 60, as measured 100 or 180 days after HCT.

We did not intend to compare renal function in the context of MA versus RIC regimens. However, Parikh and collaborators [22] reported that patients undergoing MA HCT have a greater incidence of severe acute renal failure and dialysis (12% versus 3%), when compared to recipients of NMA transplants.

In conclusion, a mild to moderate decrease in the GFR is not associated with worse survival, NRM, or TRM in patients with AML/MDS receiving RIC HCT with Flu/Mel. Prospective controlled studies analyzing the effect of the baseline renal function in patients undergoing HCT are needed.

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